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10/568,995	10/12/2006	Geoffrey Hill	250898	1774

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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,995	HILL ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-92* is/are pending in the application.

4a) Of the above claim(s) *1-51 and 62-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/12/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group III (claims 52-61-drawn to a pharmaceutical composition comprising a G-CSF derivative) in the reply filed on 03/17/2008 is acknowledged. The traversal is on the grounds that the claims of the Application are linked so as to form a single inventive concept. This is not found persuasive because as iterated in the previous Office action, compositions comprising G-CSF were known in the art. The intended use does not make the composition new or patentable.

2. The examiner has required restriction between product and process claims. Applicant elected claims directed to the product, and, if the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not

commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

The requirement is still deemed proper and is therefore made FINAL.

Status of the claims

3. Claims 1-92 are pending. Claims 1-51 and 62-92 are withdrawn as being drawn to non-elected inventions. Claims 52-61 are being examined.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 52-56 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Souza (U. S. Pat. No. 4,810,643).

Souza teaches pharmaceutical compositions comprising effective amounts of human G-CSF polypeptides together with suitable diluents, adjuvants and/or carriers useful in hG-CSF therapy. Polypeptide products taught are useful, alone or in

combination with other hematopoietic factors or drugs in the treatment of hematopoietic disorders, such as aplastic anemia or in bone-marrow transplantation (col4, lines 30-63). The polypeptides taught by Souza have part or all of the primary structural conformation (i.e., continuous sequence of amino acid residues) and one or more of the biological properties (e.g., immunological properties and in vitro biological activity) and physical properties (e.g., molecular weight) of naturally-occurring hG-CSF including allelic variants thereof. These polypeptides are of prokaryotic or eukaryotic host expression. Depending upon the host employed, polypeptides of the invention may be glycosylated with mammalian or other eukaryotic carbohydrates or may be non-glycosylated. Polypeptides also include an initial methionine amino acid residue (at position -1) (col.4, lines 4-29).

The properties of a G-CSF polypeptide are dictated by its structure and the effects of using the peptide are consequences of the structure and not of the intended use. Therefore, the pharmaceutical compositions of Souza anticipate the composition of claims 52-56 and 59 of the instant Application.

6. Claims 52-56, 59 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Arpinati et al. (Blood, 95, 2484-2490, 2000-cited by Applicant).

Arpinati et al. teach that G-CSF-treatment mobilizes lymphoid dendritic cells (DC2) but not myeloid dendritic cells (DC1) from humans treated with unpegylated human recombinant G-CSF (p. 2486, left col., line 6 to p. 2687, Right col. line 11 under the fig. 5). This would result in a use of the human N-methionyl recombinant G-CSF in

cell therapy for the induction of tolerance to hematopoietic cells and solid organ transplants (p. 2489, right col., lines 2-9).

Therefore, the claims 52-56, 59 and 61 are anticipated by Arpinati et al.

7. Claims 52-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Molineux et al. (Experimental Hematology, 27, 1724-1734, 1999-cited by Applicant).

Molineux et al. teach the use of G-CSF (both in the form of recombinant human methionyl G-CSF-Filgastrim- and N-terminal mono methoxy PEGylated Filgastrim-named FilgastrimSD/01) in compositions used to treat human volunteers or mice (Introduction; p. 1733, left col., second full paragraph).The properties of this new agent FilgastrimSD/01 include a prolonged duration of action to sustain significantly elevated neutrophil counts in hematopoietically normal mice for 5 days. Normal human volunteers showed higher than baseline ANC for around 9 to 10 days after a single injection of SD/01. Data from these normal volunteers also indicate that mobilization of CD34 cells and progenitors may occur in a more timely manner and to around the same absolute numbers as with repeated daily injections of unmodified Filgrastim. These data indicate that SD/01 represents an efficacious novel form of Filgrastim with actions sustained for between one and two weeks from a single injection (abstract and Discussion section).

As evidentiary reference, Kinstler et al. (Adv. Drug Del. Rev. 54, 477-485, 2002) disclose (fig.1) that the FilgastrimSD/01 is the mono methoxy –PEG G-CSF claimed in the instant Application.

The properties of a G-CSF polypeptide are dictated by its structure and the effects of using the peptide are consequences of the structure and not of the intended use.

Therefore, the compounds of Molineux et al. anticipate the composition of claims 52-61 of the instant Application.

8. Claims 52-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Willis et al. (Expert Opin. Biol. Ther., 2, 985-992, 2002-cited by Applicant).

Willis et al. disclose that G-CSF is used, *inter alia*, for the mobilization of peripheral blood progenitor cells for autologous and allogenic transplantation. One non-glycosilated and N-methionine bearing human recombinant G-CSF is known as Filgastrim and a PEG-Filgastrim (N-terminal mono methoxy PEGylated derivative) is used under the brand name Neulasta™, Amgen, Inc. (p. 985, abstract and section 1). The benefits of using PEGfilgastrim are disclosed as having the same or better pharmacological benefits while reducing renal clearance, cellular uptake and thus increasing the time that the protein remains effective in the circulation (p. 986, section 2).

The superior results of PEG-filgastrim use with respect to the mobilization of peripheral blood progenitor cells in humans are disclosed in section 3.2.2.2.

Therefore, the claims 52-61 are anticipated by Willis et al.

9. Claims 52-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Li EC (J. Pharmacy Soc. Wisconsin., May/June 2003, 34-39-cited by Applicant).

Li EC a pharmaceutical use of Pegfilgastrim (PEGylated form of human recombinant G-CSF (p. 35, left col., second full paragraph) in a phase III clinical trail in humans. The superior qualities of Pegfilgastrim included increases in half life, decreased degradation and decreased antigenicity (i.e., increased immunological tolerance) (p. 38, right col., lines 6-12).

The properties of a G-CSF compound used in a composition are dictated by its structure and the effects of using the compound are consequences of the structure and not of the intended use. Therefore, Li EC anticipates the claims 52-61 of the instant Application.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 52-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al. (Blood, 93, 4071-4078, 1999-cited by Applicant) in view of deHaan et al. (British J. Haematol., 110, 638-646, 2000--cited by Applicant) and in further view of view of Camble et al. (U.S. Pat. No. 5,320,840).

The claims are drawn to a pharmaceutical composition for inducing immunological tolerance when administered to a subject comprising a G-CSF derivative or biologically active fragment, homolog or variant thereof and a pharmaceutically-acceptable carrier. The G-CSF may be recombinant (human) and it may also comprise not-glycosylated N-methionyl human recombinant G-CSF. The G-CSF derivative may comprise an N- terminal methionyl residue to which a mono methoxy polyethylene glycol is covalently bound thereto.) The composition may induce greater immunological tolerance when compared with administering G-CSF to humans.

Pan et al. demonstrated that G-CSF–mobilized grafts reduce severity of acute GVHD (graft versus host disease) by disruption of cytokine cascade involved in

development of acute GVHD in mice. More importantly, G-CSF–mobilized grafts maintain their GVL (graft versus leukemia) effects through a perforin-dependent pathway. The G-CSF used was recombinant human G-CSF. The authors also teach that G-CSF mobilization offers a novel approach to the separation of GVL effects from GVHD (Abstract; Material and Methods-G-CSF treatment section; Discussion last paragraph). Pan et al. is silent about the use of a PEGylated version of the G-CSF or the use in humans.

deHaan et al. teach that the PEGylated version of the human recombinant G-CSF is more efficient in mobilization of mouse progenitor and stem cells when compared to the non PEGylated version of G-CSF (abstract). The authors also point to the substantial lengthened serum half-life and reduced renal clearance of the PEGylated version (p. 638, right col., last full paragraph).

Camble et al. teach compositions that enable a therapeutically effective polypeptide (such as G-CSF) to be continuously released over a prolonged period of time following a single administration of the pharmaceutical composition to a patient (Abstract). The compositions comprise G-CSF derivatives that PEGylated (col. 18, lines 57-65) and are designed to treat humans (col. 16, lines 42-47).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have used the PEGylated version of G-CSF (as taught by deHaan et al.) in the method of Pan et al. for treating humans, as taught by Camble et al. with a reasonable expectation of success. This is because the PEGylated version has the same biological properties as human recombinant G-CSF but better

pharmacodinamical properties and it was proved to be able to treat humans. The motivation to do so is offered by deHaan et al, which underscores the superior properties of PEGylated version of G-CSF.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/, Ph.D.
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